

Platelets: Pivotal Player in Primary Sensitization to Allergen?

Platelets have been shown to be essential for the pathogenesis of bronchial asthma and allergic inflammation, in addition to their well-established roles in thrombosis and hemostasis (1–4). Bronchial asthma is a chronic pulmonary inflammatory disease that is immunologically characterized by type 2 inflammation. It is histopathologically characterized by pulmonary eosinophil infiltration and persistent structural changes in the airway walls, called *airway remodeling*. Platelet activation in bronchial asthma in humans has been extensively documented, and it is particularly important that platelet activation is significantly associated with disease severity and decreased lung function (5, 6). Meanwhile, studies using murine models of allergic asthma have also revealed that platelets are essentially involved in the asthmatic features described above, namely pulmonary leukocyte recruitment including eosinophils, airway hyperresponsiveness, and airway remodeling (7–9). Of note, human platelets are known to express both high- and low-affinity IgE receptors on their surfaces, and pulmonary platelet recruitment and accumulation are initiated in the lung via an IgE-dependent process whereby platelets and their adherent leukocytes can migrate and enter the extravascular space (6, 10). These findings suggest that platelet activation in patients with asthma may be causally related to the pathogenesis of the

disease rather than a consequence of the inflammatory environment. However, whether platelets are involved in the initial process of allergen sensitization remains unclear.

In this issue of the *Journal*, Amison and colleagues (pp. 96–103) address this question and provide evidence that platelets are indeed necessary for efficient initial sensitization to allergen, leading to propagation of the subsequent inflammatory response to secondary allergen exposure (11). Over several decades, these authors' research group has published numerous important and seminal studies showing a biological relationship between platelet activation and allergic responses. To investigate the roles of platelets during allergen sensitization, Amison and colleagues developed an ingenious mouse model of ovalbumin (OVA)-induced asthma. In this model, platelet depletion using antiplatelet antibodies was restricted to the period of allergen sensitization.

Dendritic cells (DCs) are thought to be involved in the initial development of asthma by inducing sensitization to an inhaled allergen, and Amison and colleagues demonstrated that CD11c-positive DCs were present in the airway even before allergen sensitization, although low in number (Figure 1A). Although there was no significant change in the number of CD11c-positive DCs in the airway after allergen sensitization, it should be noted that the

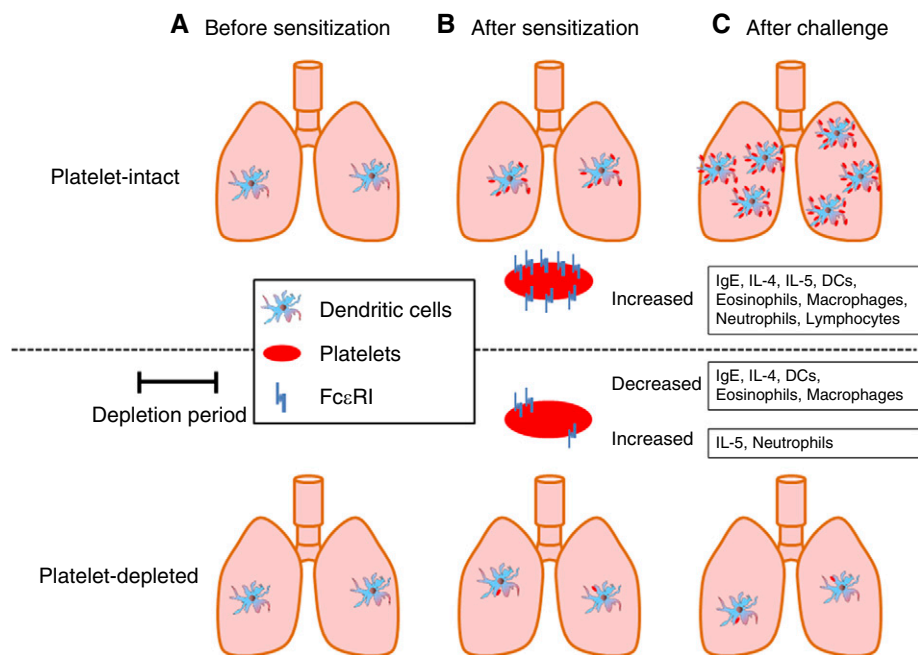


Figure 1. Schematic illustration of the roles of platelets in sensitization to allergens. To investigate the effect of platelets on sensitization to allergens, platelets were temporarily depleted before allergen sensitization (below the dashed line). (A) Dendritic cells (DCs) were present in the lung even before allergen sensitization. (B) After allergen sensitization, the number of DCs did not change, but the percentage of platelets colocalized with DCs increased (above the dashed line). Circulating platelets expressing a high-affinity IgE receptor (FcεRI) were increased during allergen sensitization (above the dashed line) but suppressed during temporary platelet depletion (below the dashed line). (C) Pulmonary recruitment of DCs, eosinophils, and macrophages, as well as colocalization of platelets and DCs in the lung, was increased after secondary allergen challenge (above the dashed line). Temporary depletion of platelets during allergen sensitization suppressed the blood IgE level, IL-4 production in the BAL fluid, and pulmonary recruitment of DCs, eosinophils, and macrophages; however, levels of IL-5 production and pulmonary recruitment of neutrophils remained high (below the dashed line).

percentage of platelets colocalized with CD11c-positive DCs was significantly increased after sensitization (Figure 1B). Moreover, this colocalization around the airway walls became even more pronounced after secondary OVA exposure via an aerosol challenge (Figure 1C). To evaluate whether platelets are involved in allergen sensitization, platelets were temporarily depleted before allergen sensitization. The platelet count had recovered before the start of secondary exposure to aerosolized OVA, and the temporary platelet depletion did not affect the circulating leukocyte count. Importantly, blood platelet expression of a high-affinity IgE receptor, FcεRI, was increased during allergen sensitization but suppressed in the recovered platelet population (Figure 1B). The authors further demonstrated that temporary depletion of platelets at the time of allergen sensitization resulted in strong effects on various subsequent immunological responses to secondary allergen challenge, including inhibition of pulmonary recruitment of eosinophils, macrophages, and CD11c-positive DCs, as well as suppression of IgE and IL-4 production (Figure 1C).

Although platelet activation in patients with asthma has long been recognized, this study shows, for the first time, to my knowledge, that platelets are essential for the initial processing of allergen *in vivo*. Together with a number of previous studies, including reports by the authors' research group, it has become clear that platelets play crucial roles in all phases of bronchial asthma, from the initial process of allergen sensitization to the allergen-dependent immune responses elicited by secondary allergen exposure. The findings and data reported by Amison and colleagues in this study are merely phenomenological, and the precise mechanisms remain unknown. However, their observations have the potential to establish platelets as a new point of focus in allergy research and are extremely important for understanding the etiological mechanism(s) leading to bronchial asthma. Furthermore, this study highlights the fundamental question of why professional antigen-presenting cells such as DCs require interaction with platelets for more efficient processing of allergen and effective induction of allergic immune responses. Interestingly, platelets from a patient with dust mite allergy were shown to be directly activated by the specific allergen but not activated by other allergens to which the patient was not sensitized (12), suggesting that platelets play a role in the allergen-specific sensitization. It was recently reported that platelets contain an alarmin cytokine, IL-33 (13), which is indispensable for innate type 2 airway inflammation (14) as well as for the pathogenesis of bronchial asthma (15). Interaction between platelets, expressing both allergen-specific FcεRI and IL-33 protein, and antigen-presenting cells may be necessary to polarize the innate immune responses toward type 2 inflammation and acquired immune responses such as allergen-specific sensitization.

In conclusion, Amison and colleagues reveal that platelets, which are essential blood immune cells responsible for thrombosis and hemostasis, are also indispensable for the allergen-specific sensitization process. The findings of this study raise various other important and intriguing questions. For example, what is the mechanism of induction of allergen-specific FcεRI on circulating platelets? And how is an "immune memory" established in a subset of megakaryocytes (precursor of platelets) that enables continued production of a population of platelets having increased expression

of the allergen-specific FcεRI? Clarification of the detailed molecular mechanisms of platelets' involvement in acquired immunity, including allergen sensitization, has the potential to lead to a deeper understanding of the pathogenesis of bronchial asthma. ■

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